

## **REMARKS/ARGUMENTS**

### **Claim Amendments**

Claims 1-55 have been cancelled and claims 56-65 have been added. Support for the new claims is found in the application as filed, for example as summarized in the table below.

<b>Claim</b>	<b>Support</b>
56	Previous claims 39 and 42
57	Previous claim 40
58	Previous claim 41
59	Previous claim 43
60	Page 18, paragraph [099]
61	Previous claim 44
62	Previous claim 46; pages 10-11, paragraphs [063], [064] and [065]; Figures 23A-23C
63	Previous claim 46
64	Previous claim 55
65	Previous claim 53

The claim amendments have been made without prejudice and without acquiescing to any of the Examiner's objections. The Applicants submit that no new matter has been entered by the present amendment and entry of the amendments is respectfully requested. The Applicants reserve the right to file any of the cancelled subject matter in a divisional patent application.

The Official Action dated June 4, 2007 has been carefully considered. It is believed that the claims submitted herewith and the following comments represent a

complete response to the Examiner's comments and place the present application in condition for allowance. Reconsideration is respectfully requested.

### **Recordation of Substance of Telephone Interview with Examiner Jagoe**

In accordance with 37 CFR §1.113(b), the Applicants submit the following recordation of the substance of a telephone interview with the Examiner that occurred on October 2, 2007. The following information is to supplement the information provided on form PTOL-413 dated October 10, 2007, prepared by the Examiner.

Present at the interview were Examiner Jagoe, Patricia Folkins (agent for the Applicants) and Micheline Gravelle (agent for the Applicants). There were no exhibits shown or demonstrations conducted during the interview. The merits of all of the currently rejected claims were discussed. Specific prior art that was discussed included Fernandez-Salguero et al. (Am. J. Hum. Genet. 57:651-660, 1995) and Draper et al. (Arch. Biochem. Biophys. 341:47-61, 1997)

Formality issues were discussed with respect to claim 60 and its lack of antecedent basis in claim 59. The Examiner pointed out that a species election was made in the application drawn to methoxsalen. The Examiner noted that no art was found for methoxsalen therefore the generic claim was searched.

With respect to the cited art, the primary reference discussed was Fernandez-Salguero et al. as the Examiner believed this to be the strongest piece of art. The Examiner's main argument was that there were a finite number of possible enzymes known to be involved in nicotine metabolism and therefore it was obvious to select inhibition of CYP2A6 for inhibiting nicotine's metabolism.

The Applicants pointed out that Draper was not citable in the present application as it was published after the Applicant's priority date of July 1996.

### **35 U.S.C. § 112, First Paragraph**

The Examiner has rejected claims 45, 46, 48 and 55 under 35 U.S.C. § 112, first paragraph for failing to meet the written description requirement. The Examiner objects to the term "CYP2A6 inhibitors having a lactone structure with a carbonyl moiety". The Examiner alleges that no other detailed, relevant characteristics are specified which would adequately describe other useful CYP2A6 inhibitors having a lactone structure with a carbonyl moiety.

In the claims submitted herewith, the Applicants have cancelled the subject matter of claims 45 and 48 and have limited the subject matter of previous claim 46 (now found in claim 63) to only specifically named compounds by removing the expressions "and related flavones", "analogs thereof" and "derivatives thereof". The Applicants submit that all of the compounds recited in the present claims are clearly defined by name, and therefore, by structure and the relevant characteristics have thus been specified. The Applicants note that claim 55 is directed to only two specifically named compounds, neither of which comprises a lactone structure with a carbonyl moiety, accordingly they submit that the Examiner's inclusion of this claim in this rejection is in error.

In light of the above, the Applicants request that the Examiner's rejection of claims 45, 46, 48 and 55 under 35 U.S.C. § 112, first paragraph be withdrawn.

### **35 U.S.C. § 112, Second Paragraph**

The Examiner has rejected claim 44 under 35 U.S.C. § 112, second paragraph as being indefinite in the recitation of the limitation "two or more of said substances". The subject matter of claim 44 is now found in claim 60 which includes the recitation "two or more of said substances which selectively inhibits CYP2A6". Claim 55, upon which claim 60 depends, contains the recitation "at least one substance which selectively inhibits CYP2A6" which provides the antecedent bases for two or more substances in claim 60.

In light of the above, the Applicants request that the Examiner's rejection of claim 44 under 35 U.S.C. § 112, second paragraph be withdrawn.

The Examiner has rejected claim 46 for its dependency on claim 45. The subject matter of claim 45 has been cancelled. The subject matter of claim 46 is now in claim 61 which is dependent on new independent claim 55. The Applicants submit that claim 55 provides proper antecedent basis for the subject matter of claim 61.

The Examiner has also rejected claim 46 for use of the expressions "analogs thereof and derivatives thereof" and "related flavones". These expressions have not been used in the claims submitted herewith.

In light of the above, the Applicants request that the Examiner's rejection of claim 46 under 35 U.S.C. § 112, second paragraph be withdrawn.

### **35 U.S.C. § 103 (a)**

The Examiner has rejected claims 39-46, 48, 52, 53 and 55 under 35 U.S.C. § 103 (a) as being obvious over Fernandez-Salguero et al. (Am. J. Hum. Genet. 57:651-660, 1995, hereinafter "Fernandez-Salguero"), Gonzalez et al. (PCT Patent Application Publication No. WO 95/34679, hereinafter "Gonzalez") and Draper et al. (Arch. Biochem. Biophys. 341:47-61, 1997, hereinafter "Draper"). The Applicants traverse this rejection for the reasons that follow.

During the above-described interview, it was the Examiner's opinion that a person skilled in the art need only choose from a finite number of possible enzymes that were suggested to be involved in the metabolism of nicotine to cotinine at the time the present application was filed. In light of this, the Examiner concluded that the selection of CYP2A6 from among this finite number of possibilities would have been obvious to try. The Applicants respectfully disagree for the reasons that follow.

According to the recent publication entitled "Examination Guidelines for Determining Obviousness Under 35 U.S.C. §103 in view of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*" (Federal Register, Vol. 72, No. 195, October 10, 2007) the finding of "obvious to try", i.e. choosing from a finite number of identified, predictable solutions, with a "reasonable expectation of success", requires the following:

- (1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;
- (2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;
- (3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and
- (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

The guidelines further state that

The rationale to support a conclusion that the claim would have been obvious is that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." [cite omitted] If any of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art. [emphasis added]

The Applicants submit that, at the time the present application was filed, the findings identified above under (1), (2) and (3) were not met in the present case. That is, for the reasons provided below, at the time the present application was filed, there was not a **recognized need in the art** to inhibit the metabolism of nicotine to cotinine;

there was not a recognized finite number of identified, **predictable potential solutions** to the inhibition of nicotine metabolism to cotinine; and there was certainly no **reasonable expectation of success** with inhibition of any of the potential enzymes.

The Examiner alleges that "both Fernandez-Salguero and Gonzalez teach the importance of CYP2A6 in the metabolism of nicotine, and recognize that the absence of CYP2A6 would inhibit the breakdown of nicotine [to] its iminium ion, and then to cotinine". The Examiner fails to recognize that, while Fernandez-Salguero and Gonzalez may suggest that CYP2A6 is involved in the metabolism of nicotine to cotinine, neither of these references teach or suggest that inhibition of CYP2A6 will translate to the inhibition of nicotine metabolism to cotinine in an individual.

It is well recognized in the art that the biological systems are complicated. In particular, the human body contains an elaborate and often redundant system of metabolic checks and balances to safeguard an individual in the event of failure in one particular system. In the present example of the metabolism of a compound by enzymes in the body, it is typical for there to be more than one pathway to break down the compound and avoid potential toxicity. The Applicants submit that this is particularly true for the metabolism of nicotine. The literature available up until the present application was filed was replete with evidence that the metabolism of nicotine to cotinine was complicated, not well-understood and certainly there was no predictable answer as to which one (if not more) of the enzymes proposed to be involved in nicotine's metabolism, should be inhibited in an individual to provide a reasonable expectation of success. In fact the Applicants submit that it was not even certain at the time the present application was filed that inhibition of the metabolism of nicotine to cotinine was a desirable avenue at all.

The Applicants submit that at the time the present application was filed, research on identification of the human CYPs involved in nicotine metabolism to cotinine had suggested several enzymes, including CYP2A6, CYP2B6, CYP2C8, CYP2C9,

CYP2D6, CYP2E1, CYP2F1 and CYP4B1 (Flammang et al., Arch. 8: 1-8, 1992; McCracken et al., Med. Sci. Res. 20:877-878, 1992, copy enclosed; Nakajima J. Drug Metabolism and Disposition 24: 1212-1217, 1996 copy enclosed; Seaton, Pharmac. Ther. 60:461-500, 1993, see Table 5. p 488, cited in the present Office Action). It is particularly noted that in 1996 (i.e. at the time the present application was first filed) Nakajima concludes that:

the enzyme responsible to cotinine formation in humans was in controversy.

Further, the review article written by Seaton highlights the complexity of nicotine metabolism and the inconclusiveness of the results from previous studies:

[N]icotine metabolism, the study of which is complicated by the existences of multiple metabolic pathways, has been, and continues to be, extensively investigated.[...] Due to large variations caused by several critical host factors, these differences in design render comparison of results exceedingly difficult, of not impossible. [emphasis added] (page 462, paragraph 1)

In addition, Seaton goes on to teach that cimetidine, an agent that inhibits the CYP450 enzymes (page 472, 4th paragraph) decreased rates of nicotine metabolism (page 473, 1st paragraph) in an individual, yet cimetidine causes little or no inhibition of CYP2A6 (Draper, cited in the present Office Action).

With respect to the documents cited in the Office Action, the Examiner alleges that Fernandez-Salguero teaches that CYP2A6 has the highest activity in the conversion of nicotine to cotinine. This is an error as Fernandez-Salguero merely references another paper as teaching that CYP2A6 has one of the highest activities in the conversion of nicotine to cotinine. Further, the Examiner alleges that Fernandez-Salguero teaches that, in human liver microsomes, a correlation was found between coumarin 7-hydroxylation, CYP2A6 protein content and oxidation of nicotine to its

iminium ion, the intermediate on route to cotinine. The Applicants note that Fernandez-Salguero does not provide any specific data in support of the Examiner's allegations. In fact, Fernandez-Salguero reports the effect of variations in the CYP2A6 gene sequence only on coumarin 7-hydroxylation. There is no direct teaching of the effect of genetic variations in the CYP2A6 sequence on the metabolism of nicotine to cotinine, nor that CYP2A6 is involved in the metabolism of nicotine to cotinine in Fernandez-Salguero.

The suggestion in Fernandez-Salguero that CYP2A6 has one of the highest activities in the conversion of nicotine to cotinine is attributed to McCracken et al. Med. Sci. Res. 20:877-878, 1992 (see page 659, column 1 of Fernandez-Salguero). The suggestion in Fernandez-Salguero that, in human liver microsomes, a correlation was found between coumarin 7-hydroxylation, CYP2A6 protein content and oxidation of nicotine to its iminium ion, the intermediate on route to cotinine, is attributed to Cashman et al. Chem. Res. Toxicol. 5:639-646, 1992 (see page 659, column 2 of Fernandez-Salguero). Copies of both McCracken and Cashman have been enclosed herewith. The Applicants submit that there is no teaching in either of these references, and therefore in Fernandez-Salguero, that CYP2A6 is a predictable solution for inhibition of the metabolism of nicotine to cotinine in an individual. In fact both of these references highlight the unpredictability of the enzymes involved in this process as shown in the following passages quoted from these papers:

McCracken, page 877, column 1:

[a]lthough it is unclear which human P450 isozymes are responsible for the metabolism of nicotine to cotinine, phenobarbitone pre-treatment is associated with increased cotinine formation [Emphasis added].

Cashman, page 645, top of 2<sup>nd</sup> column:

However, the conclusion that P-450 2A6 is largely responsible for cotinine formation does not preclude the involvement of other P-450s in this key step in human nicotine metabolism. In fact, results of another study

[Flammang, A. M., Gelboin, H. V., Aoyama, T., Gonzalez, F. J., and McCoy, G. D. (1992) Nicotine metabolism by cDNA-expressed human cytochrome P-450s. *Biochem. Arch.* 8, 1-8] suggest that other human liver P-450s (i.e. 2B6, 2C9, 2E1, 2F1, and 4B1) play a prominent role in nicotine  $\Delta^{1,5}$ -iminium ion formation. [emphasis added]

Cashman, Page 645, 2<sup>nd</sup> column:

While the human pharmacokinetics of nicotine have been extensively studied, the molecular basis for metabolism of nicotine remains unclear.

Furthermore, it is noted that Fernandez-Salguero describes certain individuals that have genetic CYP2A6 polymorphisms that completely lack coumarin hydroxylase activity, yet these individuals still have the ability to metabolize the coumarin (see pg. 655 of Fernandez-Salguero: "However, we also found three subjects genotyped as homozygous mutants (-/-) who had coumarin metabolism ratios similar to those exhibited by the heterozygous subjects.") (see also Seaton, Sections 2.3.1 Genetic variation and 2.3.2. re: large interindividual differences (p 469)). As is the case in many biological systems, this verifies that it is completely **unpredictable** that the inhibition of only one of several enzymes in a metabolic pathway will lead to an effective inhibition of metabolism of a compound in an individual.

Gonzalez merely describes genetic polymorphisms in the CYP2A6 and CYP2C9 genes. There is no specific teaching in Gonzalez that inhibition of CYP2A6 would predictably result in inhibition of nicotine metabolism to cotinine in an individual.

The Examiner alleges that Draper teaches that clotrimazole, diethyldithiocarbamate, ellipticine, ketoconazole, 8-methoxypsoralen, 4-methylpyrazole, miconazole and alpha-naphthoflavone are inhibitors of CYP2A6. The Applicants note that Draper was published in May, 1997 which is after the priority date of the present application. Accordingly, Draper is not citable against the claims of the present application. Even if Draper were citable against this application, the Applicants note

that Draper teaches that the above-mentioned compounds inhibit the hydroxylation of the 7 position of coumarin and is silent about the effects of CYP2A6 on the metabolism of nicotine. Accordingly, Draper goes no further to provide teaching that inhibition of CYP2A6 would inhibit the metabolism of nicotine to cotinine in an individual.

The Applicants submit that non-admissibility of Draper is particularly relevant to claims 62-64 submitted herewith where specific CYP2A6 inhibitors are claimed.

Accordingly, at the time the present application was filed, the Applicants submit that it was clear that there was no identified, predictable potential solution to the enzyme or enzymes involved in the metabolism of nicotine metabolism to cotinine. Due to the complexity of this biochemical process and the conflicting results, it was still unknown in 1996 if inhibition of any one or more of the enzymes suggested to be involved would result in inhibition of nicotine metabolism in an individual. This fact did not become known until the present inventors taught that by administering a selective inhibitor of CYP2A6 to human subjects, a beneficial therapeutic effect could be realized on their smoking behaviour. In particular, as reported in Example 4 and Figures 25, 26 and 27 of the present application as filed, the Applicants have demonstrated that administration of a potent and selective inhibitor of CYP2A6 to smoking patients resulted in a significant increase in plasma nicotine and a significant decrease in the subject's desire to smoke, urge to smoke and in the expectation that a cigarette would be pleasant (see page 47, paragraph [147] of the application as filed).

In light of the above, the Applicants submit that the claims submitted herewith are not obvious over the combined teachings of Fernandez-Salguero, Gonzalez and Draper and respectfully request that the Examiners rejection of claims 39-46, 48, 52, 53 and 55 under 35 U.S.C. § 103 (a) be withdrawn.

The Examiner has rejected claims 39-45, 52, 53 and 55 under 35 U.S.C. § 103 (a) as being obvious over Berkman et al. (Biochem. Pharmacol. 50:565-570, 1995, hereinafter "Berkman"), Seaton et al. (Pharmac. Ther. 60:461-500, 1993, hereinafter "Seaton") and Draper et al. (Arch. Biochem. Biophys. 341:47-61, 1997, hereinafter "Draper"). The Applicants traverse this rejection for the reasons that follow.

The Examiner alleges that Berkman teaches that CYP2A6 is the primary enzyme that transforms nicotine to nicotine  $\Delta^{1,5}$ -iminium ion. The Applicants submit that, while Berkman suggests that CYP2A6 is one of the enzymes involved in the metabolism of nicotine to cotinine, Berkman does not teach or suggest that inhibition of this enzyme will result in inhibition of nicotine metabolism to cotinine in an individual. A person skilled in the art, in reviewing the data provided in Table 1, page 568, of Berkman would see that, of the subjects for which the smoking history<sup>1</sup> was known (i.e. subjects A, B, D, I and F) those with the lowest levels of cotinine formation (i.e. patients A, B and F) were the smokers, whereas the non-smokers (i.e. patients D and I) had the highest levels of cotinine formation. Low levels of cotinine indicate that nicotine is not being metabolized to this species, a situation that would be expected to be analogous to the case where a subject has been administered an inhibitor of the primary enzyme involved in the metabolism of nicotine to cotinine. In the results presented in Berkman, these subjects were smokers, a nicotine-related disorder. In fact, the two heaviest smoker (subjects A and B) had the lowest values of catalytic efficiency ( $V_{\max}/K_{m,app}$ ) for nicotine metabolism to cotinine, suggesting that inhibition of this process would have no effect, in particular, and therefore, would not be motivated to invent a product based on this premise.

Contrary to the results presented in Berkman, the present Applicants have surprisingly found that when smoking subjects were administered a selective inhibitor of CYP2A6, plasma nicotine levels were increased, cotinine levels did not change and the subjects felt less need to smoke.

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<sup>1</sup> Table 1 of Berkman refers to Cashman et al. Chem. Res. Toxicol. 5:639-646, 1992 (copy enclosed) for the smoking histories of the listed subjects.

Further, Berkman also teaches that the calculated metabolic clearance of nicotine via cotinine in the liver is only 23% of the total clearance (page 569, column 2). Berkman goes on to suggest that

the difference between total metabolic clearance and hepatic clearance for (S)-nicotine biotransformation derives from a (yet to be discovered) metabolite or non-hepatic metabolic pathway of (S)-nicotine (page 569, column 2) [Emphasis added].

Accordingly, the teachings in Berkman that metabolism of nicotine via cotinine might only be responsible for 23% of the total metabolism of nicotine, along with the results described above regarding cotinine formation in smokers, would **not** have lead a person skilled in the art to believe that administration of a CYP2A6 inhibitor to an individual would result in inhibition of the metabolism of nicotine to cotinine in that individual. Arguably, based in the teachings in Berkman, a person skilled in the art would not have even expected that inhibition of the metabolism of nicotine to cotinine, by any route, would be therapeutically useful for the treatment of nicotine-related disorders.

Seaton is a general review of P450 enzymes and the metabolism of nicotine. Passages from Seaton are quoted above. Its overall message is that inhibition of P450 enzymes, in general, can effect nicotine metabolism however, as described above, Seaton highlights the uncertainty at the time the present application was filed in the results from studies on the metabolism of nicotine and in fact does not mention at all that CYP2A6 is the P450 enzyme responsible for the conversion of nicotine to cotinine. As described above, the teachings in Seaton also suggest that a person skilled in the art would not have even considered inhibition of the metabolism of nicotine as a viable therapeutic avenue. Therefore Seaton does not make up the above-mentioned deficiencies in the teachings of Berkman.

Once again, the Examiner alleges that Draper teach that clotrimazole, diethyldithiocarbamate, ellipticine, ketoconazole, 8-methoxypsoralen, 4-methylpyrazole, miconazole and alpha-naphthoflavone are inhibitors of CYP2A6. The Applicants note that Draper was published in May, 1997 which is after the priority date of the present application. Accordingly, Draper is not citable against the claims of the present application. Even if Draper were citable against this application, the Applicants note that Draper teaches that the above-mentioned compounds inhibit the hydroxylation of the 7 position of coumarin and is silent about the effects of CYP2A6 on the metabolism of nicotine. Accordingly, Draper goes no further to provide teaching that inhibition of CYP2A6 inhibit the metabolism of nicotine to cotinine in an individual.

Accordingly, the Applicants submit that, based on the teachings of Berkman, Seaton and Draper, a person skilled in the art would not have known that administration of a selective inhibitor of CYP2A6 would inhibit the metabolism of nicotine in an individual. At the time the present application was filed, the Applicants again submit that it was clear that there was no identified, predictable potential solution to the enzyme or enzymes involved in the metabolism of nicotine metabolism to cotinine. Due to the complexity of this biochemical process and the conflicting results, it was still unknown in 1996 if inhibition of any one or more of the enzymes suggested to be involved would result in inhibition of nicotine metabolism in an individual. As noted above, this fact did not become known until the present inventors taught that by administering a selective inhibitor of CYP2A6 to human subjects, a beneficial therapeutic effect could be realized on their smoking behaviour (*vide supra*).

In light of the above, the Applicants submit that the claims submitted herewith are not obvious over the combined teachings of Berkman, Seaton and Draper and respectfully request that the Examiners rejection of claims 39-45, 52, 53 and 55 under 35 U.S.C. § 103 (a) be withdrawn.

**Double Patenting**

The Examiner has provisionally objected to claims 39-46, 48, 52, 53 and 55 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19, 27, 39-41 and 47-49 of Applicants' co-pending application no 09/214,851.

The Applicants have submitted herewith a terminal disclaimer which renders the Examiner's rejection of 39-46, 48, 52, 53 and 55 moot.


In light of the above, the Applicants request that the Examiner's rejection of claims 39-46, 48, 52, 53 and 55 under the judicially created doctrine of obviousness-type double patenting be withdrawn.

The Applicants submit that the information provided herein is fully responsive to the Examiner's requests and invites the Examiner to contact Patricia Folkins at 416-957-1683 if any further information is needed.

Early and favorable action on the merits is awaited.

Respectfully submitted,

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Enclosures